IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mark R. Prausnitz, Jin Liu, and Thomas N. Lewis

#23
3-25

Serial No.: 09/229,226 Art Unit: 3737

Filed: January 12, 1999 Examiner: R. Smith

For: *ASSESSMENT AND CONTROL OF ACOUSTIC TISSUE EFFECTS*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-33 in the Office Action mailed September 13, 2002 in the above-identified patent application. A Notice of Appeal was mailed on January 13, 2002. A check in the amount of $160.00 for the filing of this Appeal Brief for a small entity is enclosed. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Georgia Tech Research Corporation, Atlanta, Georgia.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-33 are pending and are on appeal.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on July 24, 2002. An amendment after final rejection was mailed on December 13, 2002. In the Advisory Action mailed December 19, 2002, the Examiner indicated that this amendment would not be entered. An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method for altering cell viability or transport of chemical or biological agents (page 3, lines 25-27) into or through an internal organ, internal tissue or vessel (page 9, lines 30-32) in a human or other animal by applying acoustic energy effective to alter transport or cell viability (page 4, lines 2-9). In one embodiment, the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue, or vessel in a different tissue (claim 28 as originally filed). In another embodiment, the acoustic energy is used to kill tumor cells (page 12, lines 5-9). The acoustic energy may be used to alter transport into or out of the cell of therapeutic, prophylactic or diagnostic agents (page 9, lines 3-6).

Agents delivered to the cells or tissues (page 9, line 29 – page 10, line 4) may be detected or quantitated (page 10, lines 26-29) by removing biological fluid or molecules simultaneously, previously, or subsequently to the application of acoustic energy and assaying the biological fluid or molecules to detect or quantitate the chemical or biological agents (page 4, lines 17-20).

The transducer may be placed inside the body using invasive or minimally invasive means (page 4, lines 26-29). For example, the transducer may be placed within a blood vessel using a catheter (page 11, lines 23-25) or the transducer may be placed within a surgical incision (page 11, lines 26-27).

Treatment of cells or tissues to alter permeability, cell viability or structural integrity (page 3, lines 25-27) is achieved by administering acoustic energy to the cells or tissues at one or more frequencies (page 6, lines 15-16), measuring a property or the effect of the acoustic energy during the treatment with acoustic energy, and then using that measurement to modify continued or subsequent application of acoustic energy to the cells or tissues as needed to enhance the treatment (page 4, lines 10-14). The property of the acoustic energy to be measured can be pressure (page 14, lines 15-17) or energy input (page 15, lines 29-31) measured at one or more frequencies (page 4, lines 10-12).

Exposure to acoustic energy can make cells or tissues more permeable (page 3, line 30 – page 4, line 4). The cells or tissues may be made either partially or completely reversibly permeable (page 6, lines 28-30). The acoustic energy may also be applied to biological membranes (page 10, lines 9-11) or tissues such as the skin (page 10, lines 11-12) or blood vessels (page 10, lines 4-9). The acoustic energy may be applied to the cells or tissue in an amount effective to disaggregate or dissociate the cells or tissues (page 11, lines 3-7).

The acoustic energy is typically applied to the cells or tissues at frequencies between 1kHz and 10MHz (page 4, lines 21-22) and a peak positive pressure of up to 100 atmospheres (page 4, lines 22-23). In one embodiment, the acoustic energy may be ultrasound (page 3, line 30 – page 4, line 2; page 1, lines 14-16). The acoustic energy may be applied under conditions to

effect cavitation within or on the surface of the cells or tissues (page 7, lines 1-6). An agent which enhances transport within or permeability of the cells or tissues may also be applied in combination with the acoustic energy (page 10, lines 20-23).

Measurement of the properties of the acoustic energy may be made at one or more frequencies other than the frequency or frequencies at which the acoustic energy is applied (page 15, lines 1-7), such as frequencies corresponding to integer multiples of one-half or one-fourth of the frequency applied (page 18, lines 13-18). Measurements may also be taken at one or more frequencies in the acoustic spectrum which do not correspond to peaks in the acoustic spectrum and are taken from the broadband signal of the acoustic spectrum (page 22, lines 23-26). The acoustic energy measurement may then be analyzed using mathematical algorithms such as Fourier Transform and Fast Fourier Transform (claim 22 as originally filed).

The acoustic energy may be modified by changing an acoustic parameter such as pressure, energy, frequency, pulse length, total exposure time, duty cycle, or any combinations of these parameters (claim 23 as originally filed; page 17, lines 18-20; page 8, lines 5-8). The modifications may also be made by changing non-acoustic parameters such as temperature, fluid gas content, administration rate of molecules to be transported, sample collection rate, device position, or any combinations of these parameters (claim 24 as originally filed; page 7, lines 7-9; page 8, lines 5-8). The acoustic energy input can also be modified by interrupting the application (claim 25 as originally filed).

The claims are also directed to a device which provides a means for treating cells or tissue by administering acoustic energy to the cells or tissues (page 8, lines 25-27) at a first site to alter permeability, cell viability or structural integrity of cells or tissues at a second distant site

(page 4, lines 23-26); measuring a property or the effect of the acoustic energy during the treatment (page 8, lines 25-28); and using the measurement to modify continued or subsequent application of acoustic energy to the cells or tissues at the first site during the treatment as needed to enhance the treatment of cells or tissues at the second distant site (page 8, lines 28-30).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-25 and 27-33 are clear and definite as required by 35 U.S.C. § 112, second paragraph;

(2) whether claims 1-2, 10, 11, 14, 15, 17, 19, 21, and 23-28 were properly rejected under 35 U.S.C. § 102(e) as lacking novelty over U.S. Patent No. 6,113,559 to Klopotek ("Klopotek");

(3) whether claims 27, 28 and 30 were properly rejected under 35 U.S.C. § 102(b) as lacking novelty over U.S. Patent No. 5,445,611 to Eppstein, et al. ("Eppstein, et al.");

(4) whether claim 22 was properly rejected under 35 U.S.C. § 103(a) as obvious over Klopotek;

(5) whether claim 26 was properly rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,636,632 to Bommannan, et al. ("Bommannan, et al.") in view of Klopotek;

(6) whether claims 1-5, 8-18, 23-26, and 29 were properly rejected under 35 U.S.C. § 103(a) as obvious over Eppstein, et al. in view of Klopotek;

(7) whether claims 1-3, 5, 7, 14, 15, 18, 23, and 25-27 were properly rejected under 35 U.S.C. § 103(a) as obvious over Tachibana, et al. *Cancer Lett* 72(3): 195-199 (1993) ("Tachibana, et al.") in view of Klopotek.

(8) whether claim 6 was properly rejected under 35 U.S.C. § 103(a) as obvious over Eppstein, et al. in view of Bommannan, et al.; and

(9) whether claim 26 was properly rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,656,016 to Ogden ("Ogden") in view of Klopotek.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together as discussed below.

(8) ARGUMENTS

(a) The Claimed Invention

Ultrasound-mediated administration of drugs, genes, and other therapeutic compounds into and across cells and tissues has shown significant potential in target drug delivery. Acoustic energy is typically generated by a transducer. The structure through which the sound waves move initially determines the point at which the ultrasound generates an effect, if any. Looking at the prior art (for example, U.S. Patent No. 5,636,632 to Bommannan, et al.) one sees that the transducer generates sound waves which pass through the acoustic chamber so that they are focused at the site where an effect is desired. In this case, the transducer is applied to the surface of the skin, but the effect is actually observed within the tissues of the skin, not at the surface. This distance is actually very short however.

Similarly, acoustic energy has been shown to permeabilize cell membranes, either reversibly for introduction of a chemical or biological agent, or irreversibly so that the cells become unviable. However, the prior art methods for application of acoustic energy to alter transport into or out of cells and tissues involve *direct* application of a transducer to the tissue to be treated, typically skin. Appellants' have developed a method of *indirectly* treating cells and

tissues by applying acoustic energy to a site on the body (such as the skin) to elicit an effect in an organ, vessel, or tissue in a different location. This improvement allows for the treatment of internal organs by non-invasively placing the transducer on the surface of the skin. Furthermore, Appellants have devised a method for enhanced control of the application of acoustic energy using feedback loops which allow for adjustment of the treatment as necessary.

(b) Rejections Under 35 U.S.C. § 112, second paragraph

(i) The legal standard

The M.P.E.P. explains that the primary purpose of the § 112 definiteness requirement is "to ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement of the patent" and "to provide a clear measure of what applicants regard as the invention". (M.P.E.P. § 2173) During examination, the Examiner's focus regarding this requirement is on "whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." (M.P.E.P. § 2173.02) The M.P.E.P. identifies factors which should be considered when examining the claim language. These factors include (1) the content of the particular application, (2) the teaching of the prior art, and (3) the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made.

M.P.E.P. § 2173.05 (b) explains that "[t]he fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. § 112, second paragraph." (M.P.E.P. § 2173.05 (b)) The test for whether such language is definite "depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." (*Id.*)

(ii) Claims 1-25 and 27-33 are definite

Claim 27 defines a method of altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue, or vessel, by applying a transducer to a first site, for the administration of acoustic energy to an organ, tissue or vessel, which is located at a second distant site. Acoustic energy is administered to the targeted tissue, organ or vessel, which is at a site distant from that to which the transducer is directly applied. Dependent claim 1 is directed to the method of claim 27 further comprising the additional step of feedback regulation. Claims 31-33 are drawn to specific ways in which the transducer can be applied to the first site.

The question is whether one of ordinary skill in the art would understand what the claims mean. The first step in this analysis is to determine if any terms have any meaning other than their ordinary meaning and if they are commonly used. This being established, one must look to what is common in the art. Looking at the prior art, one sees that application of a transducer to the skin is very common. The claims differ here in that the focal point of the acoustic energy is not at the point of application of the transducer, but at a distant site. There is nothing indefinite in this regard, however.

Thus, claim 27 and its dependent claims, claims 1-25 and 28-33, are definite.

(c) Rejections Under 35 U.S.C. § 102

(i) The legal standard

Anticipation requires the disclosure, in a single prior art reference, of <u>every element</u> of the claim. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 90 (Fed. Cir. 1986).

Absence of a claimed element from a prior art reference negates anticipation. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

Scripps Clinic & Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was

not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

(ii) Rejection of Claims 1-2, 10, 11, 14, 15, 17, 19, 21 and 23-28 under 35 U.S.C. § 102(e) over Klopotek

Klopotek

Klopotek applies ultrasound to the skin for purposes of affecting cells in the underlying layers of the skin. Klopotek does not apply a transducer to the skin and observe an effect in an internal organ or internal tissue. Layers of cells within the skin are not different tissues, as is apparent from the figures in Klopotek, as well as the summary of the invention at col. 1, line 55 to col. 2, line 37. Klopotek applies a transducer to the skin to elicit an effect on the skin. Therefore Klopotek does not anticipate nor make obvious the claimed subject matter.

(iii) Rejection of Claims 27, 28, and 30 under 35 U.S.C. § 102(b) over Eppstein

Eppstein

Eppstein teaches the application of ultrasound to the skin (col. 4, lines 31-59) or mucosa, to alter transport through the skin (col. 6, lines 59-62) or mucosa (col. 7, lines 1-9). The materials being transported may come from a tissue other than the skin, but the ultrasound is focused within the skin or mucosa. Materials may be transported into or out of blood but this is achieved by altering the permeability of the vessels within the skin. Eppstein makes reference to "the stratum corneum and even the epidermis, dermis, and other tissues beneath it," at col. 9, lines 40-43, all of which are known to be part of the skin. The skin is composed of several layers of tissue, starting at the top with the stratum corneum, then the stratum lucidum, then the stratum granulosum then the statum spinosum, then the stratum basale (the epidermis), then the papillary

region, then the reticular region (the dermis), making it clear that the reference to the tissues beneath are still part of the skin. There is no mention of any internal organ or tissue. Therefore Eppstein also does not disclose the claimed subject matter.

(d) Rejections Under 35 U.S.C. § 103

(i) The legal standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must

both be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680 16 USPQ2d 1430 (Fed. Cir. 1990)

Further, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

(ii) Rejections under 35 U.S.C. § 103(a)

Claim 22 was rejected under U.S.C. § 103(a) as obvious over Klopotek. Claim 26 was rejected under U.S.C. § 103(a) as obvious over U.S. Patent No. 5,636,632 to Bommannan in view of Klopotek. Claims 1-5, 8-18, 23-26 and 29 were rejected under 35 U.S.C. § 103(a) as obvious over Eppstein in combination with Klopotek. Claims 1-3, 5, 7, 14, 15, 18, 23, and 25-27 were rejected under 35 U.S.C. § 103(a) as obvious over Tachibana, et al., Cancer Lett. 72(3):195-199 (1993) in combination with Klopotek. Claim 6 was rejected under 35 U.S.C. 103 as obvious over Epstein in combination with Bommannan, et al. Claim 26 was also rejected under U.S.C. § 103(a) as obvious over Ogden in view of Klopotek.

(iii) The prior art

Bommannan

Bommannan describes the application of ultrasound to the skin or other biological membrane to elicit an effect on the skin or biological membrane to which the ultrasound is applied. Bommannan also describes a non-invasive diagnostic technique which can be used to

sample and evaluate biological fluids. However, Bommannan makes no reference to applying a transducer to the skin and looking for an effect in an internal tissue or organ.

Tachibana, et al.

Tachibana, et al. describes the use of ultrasound *and a photoactive cytoxic agent, Photofrin II,* to kill cells. This is quite distinct from using ultrasound directly to alter cell viability at a distant location. Tachibana also fails to disclose the application of a transducer to the skin and looking for an effect in an internal tissue or organ.

Ogden

Ogden discloses administering ultrasound to the skin to enhance drug delivery through the skin. See col. 2, lines 38-58. Ogden also makes reference to a feedback loop used to monitor drug delivery amounts and temperature. However, the only membrane mentioned by Ogden is the basil membrane (col. 1, lines 57-59), which is part of the skin.

(iv) Remarks

The prior art alone or in combination fails to disclose each of the claimed limitations: (1) a method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal by (2) applying acoustic energy effective to alter transport or cell viability at a distant second site (such as an internal organ) by (3) applying a transducer to a first site (such as the skin) on the human or other animal other than where transport or cell viability is to be altered, and (4) using sampling and feedback mechanisms to control the application of the acoustic energy.

There is no reference in any of the prior art to the application of a transducer to the skin to elicit an effect in a different tissue or organ to which the transducer was not *directly* applied.

Appellants' claims read on the application of acoustic energy to a first site with the intent of eliciting an effect on a second distant site. Therefore the combination of either Bommannan or Ogden with Klopotek cannot make obvious claim 26. Similarly the combination of Eppstein with Klopotek cannot make obvious claims 1-5, 8-18, 23-26, and 29. Combination of Eppstein with Bommmannan also does not make obvious claim 6. Furthermore, the combination Tachibana with Klopotek does not make obvious claims 1-3, 5, 7, 14, 15, 18, 23, and 25-17.

The combination of the cited prior art would merely yield a method for altering cell viability or the permeability of cells and tissues which are *directly* exposed to ultrasound, by using a feedback loop for better control of the application. Appellants have clearly disclosed a method of eliciting an effect on tissues which are not easily reached or must otherwise be reached by invasive means.

Not only does the prior art fail to disclose each claimed element, but the prior art fails to provide the motivation to modify the prior art as Appellants have done. There is no teaching that the focal length of the ultrasound can be extended to pass through one or more tissues to another distant site, as defined by claims 27, 1, 3, 4, 5, 8, 10, 11, 14, and 18, to modify cell viability or permeability. Indeed all of the cited art teaches administration of ultrasound to the same tissue to which the transducer is applied, thereby teaching away from the claimed method. Moreover, although feedback is disclosed, remote feed is not as required by claims 1-25. No where in the art does one see feedback from a different tissue than the one to which the transducer is applied.

There is nothing leading one to insert the transducer to alter permeability internally as defined by claims 1-33. The examiner has completely failed to cite any art disclosing or making

obvious a method for making cells or tissues partially more permeable, much less making them reversibly permeable, as defined by claim 9.

No art has been cited to disclose the use of ultrasound to disaggregate or dissociate cells, as defined by claim 12. There is no disclosure of applying ultrasound to blood vessels, as required by claim 13. No art has been cited relating to the pressure at which the ultrasound is applied, much less specifying the peak positive pressure, as defined by claim 16. No art has been cited disclosing measuring feedback at a frequency other than the frequency at which the acoustic energy was applied, as required by claim 19; or in integer multiples of one-half or one-fourth of the applied frequency, as defined by claim 20; or from the broadband signal, as defined by claim 21. There is no disclosure of modifying acoustic energy by changing a non-acoustic parameter, as defined by claims 24 and 25.

(9) SUMMARY AND CONCLUSION

For the foregoing reasons, claims 1-33 are definite, novel, and non-obvious.

Respectfully submitted,

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Date: March 13, 2003

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Aisha Wyatt

Date: March 13, 2003

Appendix: Claims On Appeal

1. (twice amended) The method of claim 27 for treating cells or tissues to alter permeability, cell viability or structural integrity comprising

(a) administering acoustic energy to the cells or tissues at one or more frequencies ;

(b) measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and

(c) using the measurement obtained in step (b) to modify continued or subsequent application of acoustic energy to the cells or tissues during the treatment as needed to enhance the treatment.

2. (amended) The method of claim 1 wherein the property of the acoustic energy being measured in step b is one or more properties selected from the group consisting of pressure at one or more frequencies, and energy input at one or more frequencies.

3. (twice amended) The method of claim 1 wherein the acoustic energy is effective to alter permeability of the cells or tissues to a chemical or biological agent selected from the group consisting of peptides, proteins, sugars, polysaccharides, nucleotides, polynucleotide molecules, synthetic organic compounds, synthetic inorganic compounds, endogenous organic compounds, endogenous inorganic compounds and combinations and aggregates thereof.

4. The method of claim 3 wherein the agent is in a form selected from the group consisting of cells or virus particles, nano or microparticles, liposomes or other lipid vesicles or emulsions.

5. (amended) The method of claim 3 wherein the chemical or biological agent is delivered to cells or tissues.

6. The method of claim 3 wherein the chemical or biological agent is detected or quantitated, further comprising

removing biological fluid or molecules simultaneously, previously, or subsequently to the application of acoustic energy, and

assaying the biological fluid or molecules to detect or quantitate the chemical or biological agents.

7. The method of claim 1 wherein the acoustic energy is administered to kill cells.

8. (amended) The method of claim 1 wherein the cells or tissues are made more permeable by the exposure to acoustic energy.

9. (twice amended) The method of claim 8 wherein the cells or tissues are made partially or completely reversibly permeable.

10. (amended) The method of claim 1 wherein the acoustic energy is applied to biological membranes.

11. (amended) The method of claim 1 wherein the tissue is skin.

12. (amended) The method of claim 1 wherein the acoustic energy is applied to cells or tissue in an amount effective to disaggregate or dissociate the cells or tissue.

13. (amended) The method of claim 1 wherein the tissues are blood vessels.

14. The method of claim 1 wherein the acoustic energy is applied at a frequency between 1 kHz and 10 MHz.

15. The method of claim 1 wherein the acoustic energy is ultrasound.

16. The method of claim 1 wherein the acoustic energy is applied at a peak positive pressure of up to 100 atmospheres.

17. (twice amended) The method of claim 1 wherein the acoustic energy is applied under conditions to effect cavitation within or on the surface of the cells or tissues.

18. (amended) The method of claim 1 further comprising administering an agent to enhance transport within or permeability of the cells or tissues.

19. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at one or more frequencies other than the frequency or frequencies at which the acoustic energy is applied.

20. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at a frequency or frequencies corresponding to integer multiples of one-half or one-fourth of the frequency applied

21. (amended) The method of claim 1 wherein the acoustic energy is measured at one or more frequencies in the acoustic spectrum which do not correspond to peaks in the acoustic spectrum and are taken from the broadband signal of the acoustic spectrum.

22. (amended) The method of claim 19 wherein the acoustic energy measurement is analyzed using a mathematical algorithm, selected from the group consisting of Fourier Transform and Fast Fourier Transform.

23. The method of claim 1 wherein the application of the acoustic energy is modified by changing an acoustic parameter selected from the group consisting of pressure, energy, frequency, pulse length, total exposure time, duty cycle, and combinations thereof.

24. The method of claim 1 wherein the application of the acoustic energy is modified by changing a non-acoustic parameter selected from the group consisting of temperature, fluid gas content, administration rate of molecules to be transported, sample collection rate, device position, and combinations thereof.

25. The method of claim 1 wherein the application of the acoustic energy input is modified by interrupting the application.

26. (three times amended) A device comprising

(a) means for treating cells or tissue by administering acoustic energy to the cells or tissue at a first site to alter permeability, cell viability or structural integrity of cells or tissues at a second distant site;

(b) means for measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and

(c) means for using the measurement of the property of the acoustic energy to modify continued or subsequent application of acoustic energy to the cells or tissues at the first site during the treatment as needed to enhance the treatment of the cells or tissues at the second distant site.

27. (twice amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at a distant second distant site at a different tissue or an internal organ or an internal vessel in a different tissue.

28. (twice amended) The method of claim 27 wherein the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue or vessel in a different tissue.

29. (amended) The method of claim 27 wherein the acoustic energy alters transport or cell viability of tumor cells.

30. (amended) The method of claim 27 wherein the acoustic energy alters transport into or out of the cells of molecules selected from the group consisting of therapeutic, prophylactic and diagnostic agents.

31. (amended) The method of claim 27 wherein the transducer is placed inside the body using invasive or minimally invasive means.

32. (amended) The method of claim 27 wherein the transducer is placed within a blood vessel using a catheter.

33. (amended) The method of claim 27 wherein the transducer is placed within a surgical incision.

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